International Journal of Infectious Diseases 57 (2017) 79–85

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Infectious disease exposures and outbreaks at a South African neonatal unit with review of neonatal outbreak epidemiology in Africa

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ARTICLE INFO

Article history:
Received 30 November 2016
Received in revised form 17 January 2017
Accepted 23 January 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Neonates
Africa
Outbreaks
Nosocomial
Infection prevention

SUMMARY

Background: Hospitalized neonates are vulnerable to infection, with pathogen exposures occurring in utero, intrapartum, and postnatally. African neonatal units are at high risk of outbreaks owing to overcrowding, understaffing, and shared equipment.
Methods: Neonatal outbreaks attended by the paediatric infectious diseases and infection prevention (IP) teams at Tygerberg Children's Hospital, Cape Town (May 1, 2008 to April 30, 2016) are described, pathogens, outbreak size, mortality, source, and outbreak control measures. Neonatal outbreaks reported from Africa (January 1, 1996 to January 1, 2016) were reviewed to contextualize the authors' experience within the published literature from the region.
Results: Thirteen outbreaks affecting 148 babies (11 deaths; 7% mortality) over an 8-year period were documented, with pathogens including rotavirus, influenza virus, measles virus, and multidrug-resistant bacteria (*Serratia marcescens*,*Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci). Although the infection source was seldom identified, most outbreaks were associated with breaches in IP practices. Stringent transmission-based precautions, staff/parent education, and changes to clinical practices contained the outbreaks. From the African neonatal literature, 20 outbreaks affecting 524 babies (177 deaths; 34% mortality) were identified; 50% of outbreaks were caused by extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*.
Conclusions: Outbreaks in hospitalized African neonates are frequent but under-reported, with high mortality and a predominance of Gram-negative bacteria. Breaches in IP practice are commonly implicated, with the outbreak source confirmed in less than 50% of cases. Programmes to improve IP practice and address antimicrobial resistance in African neonatal units are urgently required.

Introduction

Hospitalized neonates are a vulnerable population owing to immature immunity and frequent infectious disease exposures through contact with healthcare staff, parents, other patients, equipment, and the hospital environment. Exposure events may lead to microbial colonization or infection with severe morbidity and mortality, as well as nosocomial outbreaks. Outbreaks in neonatal units (NNUs) of high-income countries occur at a rate of 10 per year.[1] The frequency of outbreaks in the NNUs of low- and middle-income countries (LMICs) is unknown, but is likely to be far higher owing to overcrowding, understaffing, and the sharing and reuse of equipment.[2] Despite these risk factors, published outbreak reports from African NNUs are infrequent and hindered by limited microbiology laboratory access and an absence of healthcare-associated infection (HAI) surveillance programmes and infection prevention (IP) resources.[2]

Point prevalence studies in high-income countries report healthcare-associated neonatal bloodstream infection (HA-BSI) as the most frequent infection type affecting hospitalized neonates,[3] although viral respiratory and gastrointestinal infections are also encountered. Given the high rates of HA-BSI reported from some African settings,[4–6] frequent outbreaks of nosocomial bacterial infection could be expected in African NNUs. The limited African neonatal HA-BSI descriptions reflect a predominance of Gram-negative pathogens and substantial antimicrobial

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http://dx.doi.org/10.1016/j.ijid.2017.01.026

resistance.[4–6] A recent systematic review of 30 neonatal outbreaks (2005–2015), identified *Klebsiella pneumoniae* (33%), *Serratia marcescens* (20%), and methicillin-resistant *Staphylococcus aureus* (MRSA) (20%) as the most common pathogens.[7] The mean outbreak duration was 10 months and the outbreak source was identified in 17/30 cases (57%): neonates transferred-in from other facilities ($n = 6$), contaminated ventilator equipment ($n = 5$), healthcare workers ($n = 4$), and colonized mothers ($n = 2$). The lack of resources for outbreak investigation (including laboratory services and molecular testing), hampers efforts to identify outbreak frequency and source in African NNUs.[7]

Reported NNU outbreak mortality rates are high, with the risk of death inversely proportional to the country income level (9–70%).[7] The highest mortality rates are documented among neonates with laboratory-confirmed Gram-negative and fungal BSI pathogens.[4,6,7] A lack of neonatal intensive care units (NICUs) and limited access to appropriate treatment for antimicrobial-resistant infections contribute to increased mortality in LMIC NNU outbreaks.

This article describes the Tygerberg Children's Hospital experience with the detection, investigation, and control of outbreaks in the NNU since 2008, in the context of published outbreak reports from other African NNUs over the last two decades.

Methods

Study setting

Tygerberg Children's Hospital in Cape Town, South Africa is a 124-bed neonatal referral centre located within a 1384-bed tertiary government hospital. The NNU provides medical and surgical care for sick and/or low birth weight (LBW, <2500 g) neonates, with prematurity, perinatal asphyxia, and neonatal sepsis being the predominant reasons for admission. The NNU consists of an eight-bed NICU (combined surgical and medical), a four-bed high-care, two high-care wards, one low-care ward, and a kangaroo mother care unit. Bed occupancy rates in the NNU range from 83% to 138%, with a high demand for NICU beds. The hospital performs around 8000 neonatal deliveries annually, with a LBW rate of 39%. Mothers with complicated pregnancies are referred in from the surrounding socioeconomically deprived communities.[8]

In the Western Cape Province, antenatal HIV prevalence increased between 2009 and 2013, from 16.1% to 16.9% (vs. 29.5% nationally).[9] Combination antiretroviral therapy (cART) has been available since 2004, with universal cART in pregnancy (irrespective of CD4 count) introduced from 2013. Between 2009 and 2011, a national prevention of mother-to-child HIV infection transmission (PMTCT) programme achieved a reduction in the Western Cape Province perinatal HIV transmission rate from 3.6% to 1.4%.[8,10]

Study period and method

Data on NNU outbreaks investigated by the infection prevention service and/or the paediatric infectious diseases team between May 1, 2008 and April 30, 2016 were collected prospectively. An outbreak was defined as any infectious disease (ID) cluster affecting two or more babies with the same pathogen within 7 days (isolated from sterile sites, with the same antibiogram for bacterial pathogens), or isolation of a single unusual or important pathogen, e.g., measles, *Pseudomonas spp.*[11] For each outbreak, the pathogen, NNU ward/s affected, number of cases and case fatality rate, the presumed or known source, and the IP measures instituted for outbreak control were documented.

Investigation for suspected neonatal sepsis

Sick neonates with any clinical, radiological, and/or laboratory features suggesting infection undergo at least one blood culture with/without accompanying cerebrospinal fluid and urine culture specimens, at the discretion of the attending clinicians. Symptoms and signs that trigger investigation for sepsis include lethargy, apnoea, need for increased respiratory support, poor feeding, temperature instability, abdominal distension, and raised white cell count or C-reactive protein, among others. Given the high prevalence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* at the study institution, the empirical treatment of hospital-acquired infection usually includes meropenem. Vancomycin is added if MRSA is considered a likely pathogen, e.g., with suspected central line or soft tissue infection. Fluconazole prophylaxis is not routinely used. Investigation for potential viral pathogens is undertaken based on clinical presentation, e.g., gastroenteritis (rotavirus and adenovirus) and respiratory tract infection (respiratory syncytial virus (RSV), adenovirus, human rhinovirus, parainfluenza virus 1/2/3, influenza virus A/B, and human metapneumovirus) using rapid assays, ELISA, or PCR panel testing.

Outbreak surveillance, investigation, and management

The hospital has an on-site unit for infection prevention and control (UIPC) that conducts laboratory surveillance for selected bacterial 'alert' pathogens: *K. pneumoniae*, MRSA, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *S. marcescens*, and *Acinetobacter baumannii*). Clinician reports of infection clusters are also an important trigger for outbreak investigation. Four IP nurse practitioners are employed (ratio 1:350 patients), with one dedicated to the neonatal, paediatric, and maternity service. Most infection clusters and outbreak alerts are initially investigated by line-listing of affected patients and a review of IP practices on the NNU. The detection of additional related cases results in an outbreak being officially declared with the assembly of an outbreak team, institution of IP measures based on the suspected source and route of transmission, and further epidemiological investigations where necessary. Institutional changes that may have influenced NNU infection rates and outbreak frequency include the installation of automated alcohol hand-rub dispensers (in 2013) and the introduction of a central line-associated BSI (CLABSI) programme in the NICU (in 2012). Other than increasing admission volumes and ongoing staff shortages, there were no significant changes in patient profile or physician practices during the study period.

Literature search terms

PubMed, Scopus, and the online outbreak database http://www.outbreak-database.com were searched using the terms "neonate", "Africa", "nosocomial", "healthcare-associated infection", and "outbreaks" for English-language papers published from January 1, 1996 to January 1, 2016. Each publication or outbreak database record was reviewed to extract the following information (when available): year of outbreak, country, neonatal setting, pathogen, number of clinical cases, deaths reported, presumed source or factors implicated in the evolution of the outbreak, and IP measures implemented for outbreak control.

Results

Over the 8 years, Tygerberg Children's Hospital NNU experienced 13 outbreaks affecting 148 babies with 11 deaths (7% mortality) (Table 1). Multidrug-resistant bacteria were the most frequent pathogens, followed by outbreaks of viral diseases

Table 1
Outbreaks affecting the Tygerberg Hospital neonatal unit (May 1, 2008 to April 30, 2016).

Outbreak year/s	Setting	Pathogen	Cases[a] (*n*)	Deaths (*n*)	Presumed or confirmed outbreak source	IP measures for outbreak control
2008	NNU	Rotavirus	58	0	Presumed introduction by an infected mother or healthcare worker	HH, CP, DP, temporary WC, VR, opening of additional NICU space for patient isolation, cohort isolation in incubators, careful disposal of baby nappies, enhanced environmental and equipment cleaning, education of staff and parents, daily screening of mothers for symptoms of gastroenteritis (6 identified)
2009	NNU	H1N1 influenza virus	5	1	Presumed introduction by an infected mother or healthcare worker	HH, DP, cohort isolation, education of staff and parents, VR, exclusion of symptomatic staff members
2010	Wards	Rotavirus	16	0	Presumed introduction by an infected mother or healthcare worker	CP, DP, HH, VR, no WC, cohort isolation in incubators, enhanced environmental cleaning, attention to handling of nappies, staff and parent education
2010	Ward	Measles virus (congenital)	1	0	Measles-infected mother during a country-wide measles outbreak	AP, cohort isolation of case and 'contacts' in incubators, designated staffing to the affected cubicle, immunoglobulin to exposed babies, measles vaccine to non-immune adults
2012	NNU	*Serratia marcescens*	12	4	Reused and inadequately decontaminated ventilator tubing	The practice of reusing ventilator tubing was stopped, hospital management approved financial expenditure for purchasing new tubing, a faulty washer-disinfector was condemned and replaced, sterile services staff were retrained on disinfection methods
2012–13	NNU	MRSA	24	0	No source identified, ascribed to non-compliance with basic IP measures	CP, HH, staff education, MRSA decolonization protocol for colonized and infected staff and neonates (chlorhexidine gluconate body washes + mupirocin intranasal ointment × 7 days), enhanced environmental cleaning
2013	NNU	MRSA	3	0	No source identified	CP, HH, staff education, cohort isolation, MRSA decolonization of cases and 'contacts' in the same cubicles
2013	NICU	VRE	2	0	No source identified	CP, HH, cohort isolation, movement of neonates within the affected wards was limited, enhanced environmental cleaning, staff education
2014	NNU	MRSA	4	0	No source identified, ascribed to non-compliance with basic IP measures	CP, HH, VR, staff education, cohort isolation, partial WC (affected cubicles were closed to new admissions), MRSA decolonization, enhanced environmental cleaning
2014	NICU	VRE	1	0	No source identified	CP, HH, cohort isolation, temporary WC of the affected NICU cubicle, enhanced environmental cleaning
2014	NICU	*Acinetobacter baumannii*	4	2	No source identified	CP, HH, cohort isolation, aseptic technique for insertion and maintenance of indwelling devices, enhanced environmental and equipment cleaning
2015	NNU	MRSA	4	0	No source identified	CP, HH, MRSA decolonization, cohort isolation, enhanced environmental cleaning
2015	NNU	*Serratia marcescens*	10	4	No source identified	CP, HH, introduced eye care protocols, emphasized aseptic technique for procedures, new cleaning protocols for shared equipment, enhanced frequency of environmental cleaning

AP, airborne precautions; CP, contact precautions; DP, droplet precautions; ESBL, extended-spectrum β-lactamase producer; HH, intensified hand hygiene; IP, infection prevention; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; NNU, neonatal unit; VR, visitor restriction; VRE, vancomycin-resistant Enterococcus; WC, ward closure.
[a] Cases = infected neonates (excludes colonized babies).

introduced into the NNU during large-scale community outbreaks. Two separate rotavirus outbreaks (involving 58 and 16 neonates, respectively) occurred in 2008 and 2010, affecting the neonatal wards and the NICU. The outbreak was investigated using line-listing, Gantt charts, weekly epidemiological curves, and submission of stool rotavirus enzyme immunosorbent rapid assays from symptomatic neonates and mothers. Containment measures in the first outbreak included temporary ward closures, prevention of transfers between wards, and cohort isolation of neonates (in incubators) on contact and droplet precautions. Mothers and staff were educated on the need for compliance with hand hygiene, precautions, and careful disposal of baby nappies, and daily symptom screening of mothers for gastroenteritis identified six incident cases of maternal transmission (confirmed on stool enzyme immunoassay (EIA)). Rotavirus 'exposed' babies (in the same room as infected babies) were screened by EIA if symptomatic and observed for at least 72 h before transfer out. The second outbreak was far smaller and more rapidly controlled (in 6 vs. 12 weeks) without any ward closures, owing to staff familiarity and better compliance with the rotavirus management protocol established in the 2008 outbreak.

The 2009 H1N1 influenza pandemic infected approximately 12 000 South Africans with 91 reported deaths.[12] Pregnant women were especially severely affected, with the ICU capacity to ventilate critically ill pregnant women at Tygerberg Hospital rapidly exceeded.[13] Nosocomial transmission of H1N1 influenza was confirmed in five neonates (three mothers and one healthcare worker tested positive for H1N1), with a further four 'exposed' babies. The five infected babies had a median hospital stay of 20 days at the time of laboratory testing, with a median gestational age of 28 weeks and weight of 1130 g; all were treated with oseltamivir and required NICU admission. One premature baby died from necrotizing enterocolitis (NEC) 3 days after completion of oseltamivir therapy.[14] Droplet precautions, cough etiquette, hand hygiene compliance, cohort isolation of infected/exposed babies, visitor restriction, and exclusion of symptomatic staff members was instituted. The outbreak highlighted a shortage of patient isolation facilities, particularly in the NICU, and reinforced the importance of annual staff influenza vaccination.

During a country-wide measles outbreak in 2009/2010, with over 30 000 confirmed cases nationally, a case of congenital measles was identified on a neonatal ward. A 33-week gestation neonate developed a maculopapular rash on day 4 of life. The history of maternal illness had not been available at the time and a differential diagnosis of enteroviral infection, phototherapy rash, and congenital measles was considered. Urine and a throat swab were positive for measles on PCR; subsequently measles serology was IgM-positive for the mother and baby. Immediate IP measures

implemented were airborne precautions, cohort isolation, and designated staffing to the affected neonatal cubicle. Immunoglobulin (Intragam) was given to exposed babies and measles vaccine was provided to non-immune healthcare workers and parents.

Of the nine bacterial outbreaks including *S. marcescens* ($n = 2$), *A. baumannii* ($n = 1$), MRSA ($n = 4$), and vancomycin-resistant *Enterococcus faecium* (VRE; $n = 2$), only one had definitive identification of the outbreak source. An *S. marcescens* outbreak that affected 12 premature neonates (with four deaths) between July and October 2012 was ascribed to the reuse and inadequate reprocessing of ventilator tubing. The outbreak investigation included rapid case identification with line-listing (revealing that 11/12 cases had been ventilated) and cultures of potential sources (used and re-processed, re-packaged 'clean' ventilator circuits). Clinical isolates and *S. marcescens* isolated from ventilator tubing were genotyped using pulsed-field gel electrophoresis (PFGE) identifying a single major clone. Transition to single-use ventilator circuits, heightened hand hygiene compliance, and enhanced environmental cleaning terminated the outbreak.

The first NNU outbreaks of VRE occurred in 2013 and 2014. VRE was isolated from two NICU patients (from a tissue specimen after surgery for NEC in one case and from blood culture in the other). Two further NICU patients grew VRE from catheter tips but not from peripheral blood cultures. The outbreak measures implemented included the formation of an outbreak team, screening of patients in the NICU, contact precautions and cohort isolation of cases and colonized patients, enhanced environmental cleaning, limiting of patient transfers, and staff/parent education with emphasis on hand hygiene. Targeted active screening for VRE colonization was initially conducted on 19 infants (16% carriage prevalence) and a month later on 12 infants (67% carriage), including five initially VRE screen-negative neonates who became newly colonized, suggesting a breakdown in transmission-based precautions. One infected baby remained VRE colonized for 9 months after the outbreak. None of the environmental screening swabs ($n = 14$) cultured VRE. The *vanA* gene was detected in all clinical isolates and PFGE analysis distinguished nine pulsotypes with one predominant clone. In 2014, VRE was re-introduced into the NICU through transfer-in of a premature infant with NEC and ileal perforation from another hospital. Four contacts (babies in the same ICU room) were screened (all negative) and kept on strict contact precautions; the affected ICU cubicle was closed to new admissions. Isolation precautions were quickly and successfully implemented given staff familiarity with the IP measures used during the previous outbreak.

Four outbreaks of MRSA occurred between 2012 and 2015, affecting 24 neonates in 2012/13 and 11 babies in the subsequent three outbreaks, with no deaths. The 2012/13 outbreak included MRSA BSI ($n = 13$), conjunctivitis, and skin and soft tissue infections, which occurred over a 16-week period with ongoing MRSA colonization between clusters. Screening identified MRSA carriage in 16/140 babies in the neonatal unit (11%). Staff screening was performed from outbreak week 8 because of ongoing MRSA transmission, with a 1% positivity rate (2/208). Staff screening was very unpopular, labour-intensive, and costly, with a low yield. Mothers were not screened for MRSA carriage (largely owing to cost implications and the lower risk of transmission, since the mothers only cared for their own babies and were discouraged from touching other babies). IP measures implemented included contact precautions, staff education, and MRSA decolonization of infected/colonized neonates and staff with chlorhexidine gluconate body washes and mupirocin intranasal ointment for 7 days. The pharmacy staff were particularly concerned about topical use of chlorhexidine gluconate in neonates (particularly in LBW babies). As a compromise, daily washes with 0.25% chlorhexidine gluconate were used, with no adverse events reported among the 24 infected and 16 colonized babies. In subsequent MRSA outbreaks, early identification of cases and prompt implementation of isolation measures helped to restrict the size of the outbreaks.

In 2015, four neonates in the NICU developed *A. baumannii* HA-BSI (two babies died). The outbreak investigation utilized line-listing and observation of clinical practices in the NICU, noting severe shortages in clinical and support staff preceding the outbreak. IP measures included contact precautions, hand hygiene, cohort isolation, aseptic technique for insertion and maintenance of indwelling devices, and enhanced environmental and equipment cleaning. Early identification of the outbreak and immediate implementation of strict contact precautions helped to contain the outbreak, together with improved staffing allocation in the NICU.

Table 2 lists the lessons learned in investigation and control during the 8 years of experience managing outbreaks in an NNU in a middle-income country.

Twenty published outbreak reports from African NNUs over the last two decades were identified, with the majority from Sub-Saharan Africa ($n = 16$), including South Africa ($n = 12$) (Table 3).[15–33] Very few of these published reports included an outbreak definition, but those that did usually cited an outbreak as a single pathogen affecting two or more patients with a temporal and spatial link (between 7 and 10 days, occurring on the same ward or unit). One-third of reports described outbreaks restricted to NICU settings. Outbreak pathogens were predominantly bacterial, with high rates of antimicrobial resistance. ESBL-producing *K. pneumoniae* was the most common outbreak isolate ($n = 10$), followed by multidrug-resistant *A. baumannii* ($n = 3$). Twenty percent of outbreaks (4/20) were associated with the introduction of a viral pathogen into the NNU from the community, including rotavirus, norovirus, RSV, and influenza virus. The 20 outbreaks affected 524 babies resulting in 177 deaths (34% case fatality rate), although three studies did not report the number of neonatal deaths. The outbreak source was identified in 50% of cases: infusates (glucose, intravenous fluids, parenteral nutrition) ($n = 5$), healthcare worker hands ($n = 4$), the environment (mattresses, radiant warmers, suction catheters and bottles, milk buckets) ($n = 2$), vectors (cockroaches) ($n = 1$), and other patients (RSV) ($n = 1$); some outbreaks involved multiple sources of infection. Although some publications did not report on the methods used to achieve outbreak control, commonly used measures included enhanced hand hygiene, environmental cleaning, ward closure, cohort isolation, and the introduction of aseptic handling of intravenous infusions.

Discussion

Given the reported frequency of NNU outbreaks in high-resource settings, it can be concluded that NNU outbreaks in Africa are likely grossly under-identified and under-reported, even at the present study institution. Using the expected annual rate of 10 outbreaks per NNU,[1] at least 80 outbreaks at Tygerberg Hospital should have been identified for the study period. It is likely, therefore, that even in this relatively well-resourced setting (with access to laboratory investigations, IP and ID services), NNU outbreaks are missed or undocumented.

In the two outbreaks in which strain-typing was utilized (*S. marcescens* (2012) and VRE (2013)), the use of expanded laboratory testing was instrumental in linking additional cases retrospectively and identifying the outbreak source. This institution's high HA-BSI rate (particularly for 'endemic' *K. pneumoniae* BSI) suggests ongoing bacterial transmission with small infection clusters where epidemiological relatedness is not immediately apparent (in the absence of molecular typing). In further support of this hypothesis is the fact that not a single *K. pneumoniae* outbreak

Table 2
Best practices in neonatal outbreak investigation for low- and middle-income countries.

1. Identify an outbreak or potential outbreak as early as possible (early identification is made possible by means of routine surveillance) and alert IPC staff, clinicians, and microbiologists who communicate with each other on a continual basis.
2. Take prompt action to identify all cases and contacts. Create a case definition to identify cases and amend the definition as the investigation into the outbreak progresses. Clearly define who can be regarded as contacts and base this decision on a high (substantial) risk of exposure to the case(s). Keep track of all the contacts from as early as possible. Write down all the relevant details. This is cumbersome but most often comes in handy later when contacts become infected.
3. Implement appropriate isolation measures immediately. This includes limited movement of cases and contacts and closure of affected rooms for new admissions. Elevated (stricter and more extensive) isolation precautions over and above precautions that are usually put in place for a single isolation case are often required and are usually effective in outbreak control. Cohort cases and contacts. Ensure that the appropriate personal protective equipment (PPE) and other supplies are available. Keep the minimum of supplies inside isolation rooms; e.g. one box of gloves per crib only.
4. Review isolation measures on a daily basis with the staff on duty. Include the night shift staff as well as the housekeeping and administrative staff. Give feedback about progress being made with the outbreak and emphasize the need for continued isolation precautions to keep staff motivated. Also explain the isolation measures to parents/caregivers and make sure they understand what is expected of them.
5. Draft a protocol to give guidance for the management of the outbreak. The protocols must be short (one page), easy to read, and must contain specific actions to be taken. Laminate these posters and display them in the isolation rooms where they are visible.
6. Plot cases and their location, movement, and other relevant data such as dates of positive isolates on a timeline or Gantt chart. This will help to identify the index case, possible source of the outbreak, and the clinical areas involved in the outbreak.
7. Calculate the incidence rate and plot the number of new cases on a histogram so that the progress of the outbreak can be monitored.
8. Have regular (daily if needed) meetings with hospital management, infection control, microbiology, infectious diseases, clinicians, and nursing managers to give feedback about the progress of the outbreak, isolation measures, the situation in the affected areas, and plans to continue clinical care of neonates not part of the outbreak. Also keep neighbouring hospitals informed. Communication is a key measure.
9. Ensure that isolation precautions are maintained when cases or contacts have to go for surgery or when cases and contacts are transferred to other healthcare facilities.
10. Monitor people entering the isolation rooms (e.g., consultants and allied health professionals such as dieticians and radiographers), since they may not be aware of the outbreak. Make sure that they are informed and adhere to the isolation precautions.
11. Make sure that non-compliance with the isolation protocol is addressed as soon as possible and that the reason for the non-compliance is investigated.
12. Screen staff only as a last resort and when the outbreak investigation suggests that the source of the outbreak may be due to staff carriage.
13. Screen neonates to determine carrier status when dealing with outbreaks of VRE and carbapenem-resistant *Enterobacteriaceae*.
14. Do environmental sampling only when the outbreak investigation suggests the likelihood of environmental sources of the outbreak.
15. Use a checklist for terminal cleaning of the isolation rooms and ensure that the terminal cleaning of the rooms is supervised.

IPC, infection prevention and control; VRE, vancomycin-resistant Enterococcus.

has been documented since 1996, despite this being the most frequent NNU HA-BSI pathogen, i.e., implying that 'endemic' BSI pathogens like Klebsiella may actually represent propagation of several linked infection clusters/outbreaks.

Another important difference from the Tygerberg NNU experience is the absence of *S. marcescens* in the African NNU outbreak literature. There is growing evidence of *S. marcescens* as an important neonatal pathogen globally, with substantial associated mortality[4] and long-term neurodevelopmental morbidity documented among patients at the study institution.[34] Gram-positive organisms (VRE and MRSA) are also notably absent from the African NNU outbreak literature, whereas they were relatively common outbreak pathogens at Tygerberg, albeit with low mortality. Furthermore, all reports of viral pathogen outbreaks came from South Africa, possibly reflecting easier access to virology laboratory services. Although there was no obvious influence of seasonality for bacterial outbreaks, the viruses causing outbreaks (rotavirus and influenza virus) occurred during the usual southern hemisphere peak transmission seasons for each pathogen.

Outbreak-associated mortality at Tygerberg was substantially lower than the mortality at the other African NNUs (7% vs. 34%), and even lower than mortality reported from high-income countries in a recent systematic review (9%). The availability of NICU facilities, an excellent laboratory, and IP service, as well as access to broad-spectrum antibiotics (particularly carbapenems), were probably important factors in containing outbreak size and limiting mortality at the study institution.

In the 20 African NNU outbreak reports included in this review, many supplied very limited information on the IP measures implemented. Future outbreak reports should include detailed descriptions of interventions utilized, to expand the knowledge of control strategies and their success in low-resource settings. In addition, increased reporting of African NNU outbreaks will provide clearer estimates of the continent's outbreak burden and pathogen spectrum. Additional data on the epidemiology of HA-BSI in African NNUs is also urgently required to inform empiric antibiotic neonatal regimens. Strengthening of laboratory services and the ability to conduct HAI surveillance in Africa will support both a better understanding of epidemiology and ability to investigate/report outbreaks. In particular, increased access to molecular typing services in African laboratories would be particularly helpful to integrate epidemiological and clonality data during the investigation and control of neonatal outbreaks.

The value of detailed outbreak investigation, institutional preparedness, and support of clinician leaders and hospital management in enforcing IP measures, cannot be overstated. Outbreaks on the NNU and especially in the NICU, always present a crisis because they affect bed availability. In most low-resource settings, ward closure during outbreaks is seldom implemented, as diversion of neonatal admissions is often not possible. Given this reality, cohort nursing and 'isolation' in incubators (as a physical barrier) are practical measures for outbreak management in African NNUs. Dealing with an NNU outbreak is a complex process with multifactorial challenges to address, in addition to standard measures of case, contact, and source identification and the implementation of transmission-based precautions. These challenges include the high number of 'contacts' as a result of constant movement of babies across the NNU platform; pressure to continue service delivery while containing the outbreak; insufficient isolation space; staff shortages preventing the dedicated allocation of staff to nurse infected/colonized babies; insufficient equipment to allow for dedicated use; difficulty in ensuring adequate disinfection of shared items; and staff fatigue with protocols and personal protective equipment (PPE) recommendations. Notwithstanding these challenges, in the authors' experience most outbreaks have been terminated by a combination of increased hand hygiene compliance rates, strict adherence to precautions, cohort isolation, enhanced environmental cleaning, and staff education.

In conclusion, outbreaks in hospitalized African neonates are frequent but under-reported, with high mortality and a predominance of Gram-negative bacteria. Breaches in IP practice are commonly implicated and the outbreak source is confirmed in less

Table 3
Published outbreaks affecting hospitalized African neonates (January 1, 1996 to January 1, 2016).

First author	Outbreak year/s	Country	Setting	Pathogen	Cases[a] (*n*)	Deaths (*n*)	Presumed or confirmed outbreak source	IP measures for outbreak control
Ben-Hamouda[15]	1996	Tunisia	Ward	*Klebsiella pneumoniae* ESBL	40	NR	Ward environment	NR
Newman[16]	1996	Ghana	NICU	Salmonella group G	6	0	Mattresses/radiant warmer	WC
Cotton[17]	1996	S. Africa	Ward	*Klebsiella pneumoniae* ESBL	32	15	Cockroaches in vinyl wall covering	WC, HH, removal of vinyl wall coverings, fumigation, patient screening
Pillay[18]	1996	S. Africa	Ward	*Klebsiella pneumoniae* ESBL	33	13	Unknown	WC, HH, patient isolation, enhanced environmental cleaning
Pillay[19]	1997	S. Africa	NICU	*Acinetobacter baumannii* (MDR)	9	2	Suction catheters and bottles	WC, HH, single-use catheters for suctioning
van Nierop[20]	1998	S. Africa	NICU	*Enterobacter cloacae*	12	9	Intravenous infusions, hands of staff	HH, discarded all intravenous solutions
Gregersen[21]	1998	S. Africa	NICU	*Klebsiella pneumoniae* ESBL	6	2	Unknown	HH
Jeena[22]	1999	S. Africa	NICU	*Acinetobacter baumannii* (MDR)	5	NR	Presumed environmental source	WC, HH, cohort isolation, patient screening
Moore[23]	2001	Egypt	NICU	Predominantly *Klebsiella pneumoniae* ESBL	88 (R), 24 (P)	59 (R)	Intravenous glucose preparations	Reviewed aseptic preparation of intravenous fluids, HH
Bouallègue-Godet[24]	2002	Tunisia	NN unit	*Salmonella enterica* serotype Livingstone ESBL	16	2	Not identified, possible environmental	HH, patient isolation, enhanced environmental cleaning
Boukadida[25]	2002	Tunisia	NICU	*Klebsiella pneumoniae* ESBL	14	14	Contamination of intravenous infusions, poor hand hygiene	NR
Marais[26]	2002/3 2004	S. Africa	NN unit	*Klebsiella pneumoniae* ESBL	17 10	9 6	Intravenous supplements	Aseptic preparation of intravenous fluids, HH, general IP measures
Moodley[27]	2005	S. Africa	Ward	*Klebsiella pneumoniae* ESBL	26	22	Intravenous glucose preparations	HH, stopped use of multi-dose vials
Visser[28]	2006	S. Africa	Kangaroo Care ward	RSV	23	2	RSV identical strain identified from child on paediatric ward	NR
Eibach[29]	2007–2012	Ghana	Ward	*Klebsiella pneumoniae* ESBL (4 clusters)	20	NR	NR	NR
Holgate[14]	2009	S. Africa	NN unit	H1N1 influenza	5	1	Infected staff and patients	Cohort isolation
de Villiers[30]	2010	S. Africa	NN unit	Rotavirus	44	9	Proportion of community-acquired vs. nosocomial disease NR	NR
Mshana[31]	2010	Tanzania	Ward	*Enterobacter cloacae* ESBL	17	6	Contaminated milk bucket	HH, enhanced environmental cleaning
Mshana[32]	2010	Tanzania	NN unit	*Klebsiella pneumoniae* ESBL (3 clusters)	28 26 6		Possible common source, colonized staff	NR
ProMed Mail[33]	2010	S. Africa	Ward	Norovirus	17	6	Suspected infected mother or staff member	NR

ESBL, extended-spectrum β-lactamase producer; HH, hand hygiene; IP, infection prevention; MDR, multidrug-resistant; NICU, neonatal intensive care unit; NN unit, neonatal unit admitting inborn and outborn babies <4 weeks of age; NR, not reported; P, prospective; R, retrospective; RSV, respiratory syncytial virus; S. Africa, South Africa; WC, ward closure.

[a] Cases = infected neonates (excludes colonized babies).

than 50% of cases. Programmes to improve outbreak surveillance/reporting and address lapses in IP in African NNUs are urgently required.

Funding

None.

Conflict of interest

No conflict of interest to declare.

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